(02)

Evaluation of retinal microcirculation in diabetic patients using optical coherence tomography angiography

Ocena mikrokrążenia siatkówkowego u chorych na cukrzycę za pomocą angiografii optycznej koherentnej tomografii

Maria Jędrzejak, Piotr Loba, Magdalena Kucharczyk-Pospiech, Monika Spychała, Irena Topolska, Michał Wilczyński

Department of Ophthalmology, Medical University of Lodz, Poland
Head: Professor Wojciech Omulecki, MD PhD

Abstract: Purpose: The aim of this study was to compare the length and the area of the retinal vascular network in diabetic and healthy eyes by optical coherence tomography angiography.

Material and methods: Ninety eyes of 49 patients with type 2 diabetes and non-proliferative diabetic retinopathy and 70 eyes of 35 healthy volunteers were enrolled in a prospective, observational study. All subjects were examined using optical coherence tomography (RTVue XR Avanti; Optovue). En-face optical coherence tomography angiography images of the superficial and deep capillary plexus, outer retina and choriocapillaris were evaluated using the ImageJ software. The regularity of the vascular network, a subjectively evaluated capillary density, the presence of vascular loops, microaneurysms, ischemic areas, intraretinal microvascular abnormalities and neovascularizations were all evaluated based on angioflow scans.

Results: The superficial retinal capillary network area was significantly ($p < .0001$) smaller in diabetic patients (22.257 ± 6.316 pixels) than in healthy subjects (28.355 ± 3.793 pixels). The superficial retinal capillary network length was significantly ($p < .0001$) smaller in diabetic patients (9.313 ± 2.790 pixels) than in healthy subjects (11.360 ± 1.809 pixels). The deep retinal capillary network area was significantly ($p < .0001$) smaller in diabetic patients (32.134 ± 8.926 pixels) than in healthy subjects (41.318 ± 5.247 pixels). Similarly, the deep retinal capillary network length was significantly ($p < .0001$) smaller in diabetic patients (14.282 ± 3.416 pixels) than in healthy subjects (16.909 ± 1.619 pixels). Morphological vascular anomalies are more common in patients with diabetes.

Conclusions: Optical coherence tomography angiography offers non-invasive monitoring of the retinal microcirculation in diabetic patients. Capillary length and area are easily measurable parameters.

Key words: diabetic retinopathy, type 2 diabetes, microcirculation, AngioVue SOCT, OCT angiography.

Abstrakt: Cel: ocena porównawcza długości i powierzchni naczyń krwionośnych siatkówki u chorych na cukrzycę i u osób zdrowych za pomocą angiografii optycznej koherentnej tomografii

Materiał i metody: w pracy prospektywnej zbadano 90 oczu u 49 chorych na cukrzycę typu 2. z retinopatią nieproliferacyjną oraz 70 oczu u 35 zdrowych ochotników. Wszystkich pacjentów zbadano za pomocą angiografii optycznej koherentnej tomografii.

Skany angiografii optycznej koherentnej tomografii powierzchownego i głębokiego splotu naczyń, zewnętrznych warstw siatkówki i warstwy choriokapilar zostały przetworzone programem ImageJ. Na podstawie skanów w trybie „angioflow" oceniono regularność sieci naczyń, subiektywnie oceniono gęstość sieci naczyń, obecność pętli naczyniowych, mikrotętniaków, obszarów niedokrwienia, śródsiatkówkowych nieprawidłowości drobnonaczyniowych oraz neowaskularyzacji.

Wyniki: u chorych na cukrzycę całkowita powierzchnia naczyń krwionośnych w powierzchownych warstwach plamki była istotnie mniejsza ($22{,}257 \pm 6{,}316$ pikseli) niż u osób zdrowych ($28{,}355 \pm 3{,}793$ pikseli) ($p < 0{,}0001$). Całkowita długość naczyń krwionośnych w powierzchownych warstwach plamki była istotnie mniejsza u chorych na cukrzycę ($9{,}313 \pm 2{,}790$ pikseli) niż u osób zdrowych ($11{,}360 \pm 1{,}809$ pikseli) ($p < 0{,}0001$). Również całkowita powierzchnia naczyń krwionośnych w głębokich warstwach plamki była istotnie mniejsza u chorych na cukrzycę ($32{,}134 \pm 8{,}926$ pikseli) niż u osób zdrowych ($41{,}318 \pm 5{,}247$ pikseli) ($p < 0{,}0001$). Podobnie całkowita długość naczyń krwionośnych w głębokich warstwach plamki była istotnie mniejsza u chorych na cukrzycę ($14{,}282 \pm 3{,}416$ pikseli) niż u osób zdrowych ($16{,}909 \pm 1{,}619$ pikseli) ($p < 0{,}0001$). U chorych na cukrzycę częstsze były też nieprawidłowości morfologii naczyń.

Wnioski: angiografia optyczna koherentna tomografia umożliwia nieinwazyjne monitorowanie stanu mikrokrążenia siatkówki u chorych na cukrzycę. Długość i powierzchnia sieci naczyń są mierzalnymi wskaźnikami stanu naczyń krwionośnych.

Słowa kluczowe: mikrokrążenie, cukrzyca typu 2., retinopatia cukrzycowa, AngioVue SOCT, angiografia OCT.

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Introduction

A recently developed method of optical coherence tomography angiography (OCT-A) enables a non-invasive assessment of retinal vasculature within the macular area (1). The technique seems to be the most valuable in patients requiring repeated examinations such those with diabetic retinopathy (DR). The advantages and disadvantages of the OCT-A, as compared to fluorescein angiography (FA) (which is currently a gold standard in such patients) have been reported recently (2, 3). One of the most underlined advantages of the new technique is its non-invasiveness and high resolution (2). The acquired images offer superior quality in imaging microvascular network around the fovea and thus reveal even small abnormalities and vascular irregularities. Detail visualization is much better than in the FA (4). As a result, it is possible to detect very early stages of diabetes-related microvascular complications. The purpose of this study was to assess retinal vascular network length and area using spectral OCT-A in patients with diabetes and to compare these values with healthy non-diabetic subjects.

Material and methods

The analyzed data was gathered prospectively from a non-randomized consecutive series of patients in a prospective, observational study. All patients gave an informed consent to participate in the study. All tenets of the Declaration of Helsinki were followed for all study protocols. The study was approved by the Bioethics Committee of the Medical University of Lodz (approval no. RNN/330/17/KE).

Group 1 (subjects) consisted of 90 eyes of 49 patients with type 2 diabetes and clinically evident non-proliferative diabetic retinopathy (NPDR) without diabetic macular edema (DME). This group included 28 men (57%) and 21 women (43%), aged from 31 to 103 years old (mean age was 66 $\pm$ 13 years old). There were 46 right and 44 left eyes enrolled.

Group 2 (controls) consisted of 70 eyes of 35 healthy volunteers without diabetes. This group included 32 women (92%) and 3 men (8%), aged from 35 to 70 years old (mean age was 52 $\pm$ 9 years old). There were 35 right and 35 left eyes enrolled.

The exclusion criteria were any previous ocular surgery or laser procedures, as well as any present or previous ocular disease. All patients underwent an optical coherence tomography (OCT) examination using a high-speed 840-nm-wavelength spectral-domain optical coherence tomography (SC-OCT) device (RTVue XR Avanti; Optovue).

Retinal capillaries

En-face OCT-A images of the superficial capillary plexus, deep capillary plexus, outer retina and choriocapillaris were used. Retinal capillary network was analysed based on angioflow scans. We used the same type of scans in all patients, showing black vessels on white background in a 3 x 3 mm square area (all images had 304 x 304 = 92.416 pixels). As the software provided by the OCT manufacturer does not enable measuring the parameters of the capillary network, graphical freeware analysis software ImageJ was used, and the following steps were taken. First, we wanted to evaluate the combined area of all visible capillaries. Therefore, the grayscale image (Fig. 1A) was converted to black and white only (Fig. 1B), a histogram was generated and a mean and a standard deviation were calculated (Process – Binary – Make binary – Analyze – Histogram). Then, the number of black pixels was counted (Histogram – List), which corresponds to the total area of capillaries. Next, we wanted to calculate the combined length of visible capillaries, whilst disregarding their width. In order to do so, the image had to be converted to single-pixel lines ("skeletonized") (Fig. 1C), a histogram was generated and a mean and a standard deviation were calculated (Process – Binary – Make binary – Analyze – Histogram). Then, the number of black pixels was counted (Histogram – List), which corresponds to the total length of capillaries.

Morphological changes

In order to evaluate the presence of any morphological changes of the retina, angioflow scans of the superficial and deep

Fig. 1. Angioflow OCT image transformation. Superficial capillary network is shown. First, the grayscale image (A) is converted to black and white only (B) and the number of black pixels is counted, which corresponds to the total area of capillaries. Next, the image has to be converted to single-pixel lines ("skeletonized") (C) and the number of black pixels is counted, which corresponds to the total length of capillaries.

Ryc. 1. Przekształcenia obrazów w trybie „angioflow" OCT. Pokazano powierzchowny splot naczyniowy. Na początku obraz w skali szarości (A) został przekształcony na wyłącznie czarno-biały (B), następnie policzono liczbę czarnych pikseli, to odpowiadało całkowitej powierzchni naczyń. Później obraz został przekształcony do linii o grubości jednego piksela (C), po tym policzono liczbę czarnych pikseli odpowiadającą całkowitej długości naczyń.

capillary plexus were used (Fig. 2). The presence of the morphological vascular changes was noted and graded. Subjective grading scale was used: the regularity of the superficial capillary plexus was evaluated as regular or irregular and subjectively evaluated capillary density was estimated as dense, medium dense or rare, based on comparison with average scans of a healthy person. Presence of vascular loops, microaneurysms, ischemic areas, intraretinal microvascular abnormalities (IRMA) and neovascularization (NVE) were noted.

Statistical analysis

Statistical analysis was done using parametric tests. The between-group differences were determined using a two--tailed student T-test for independent samples. All calculations

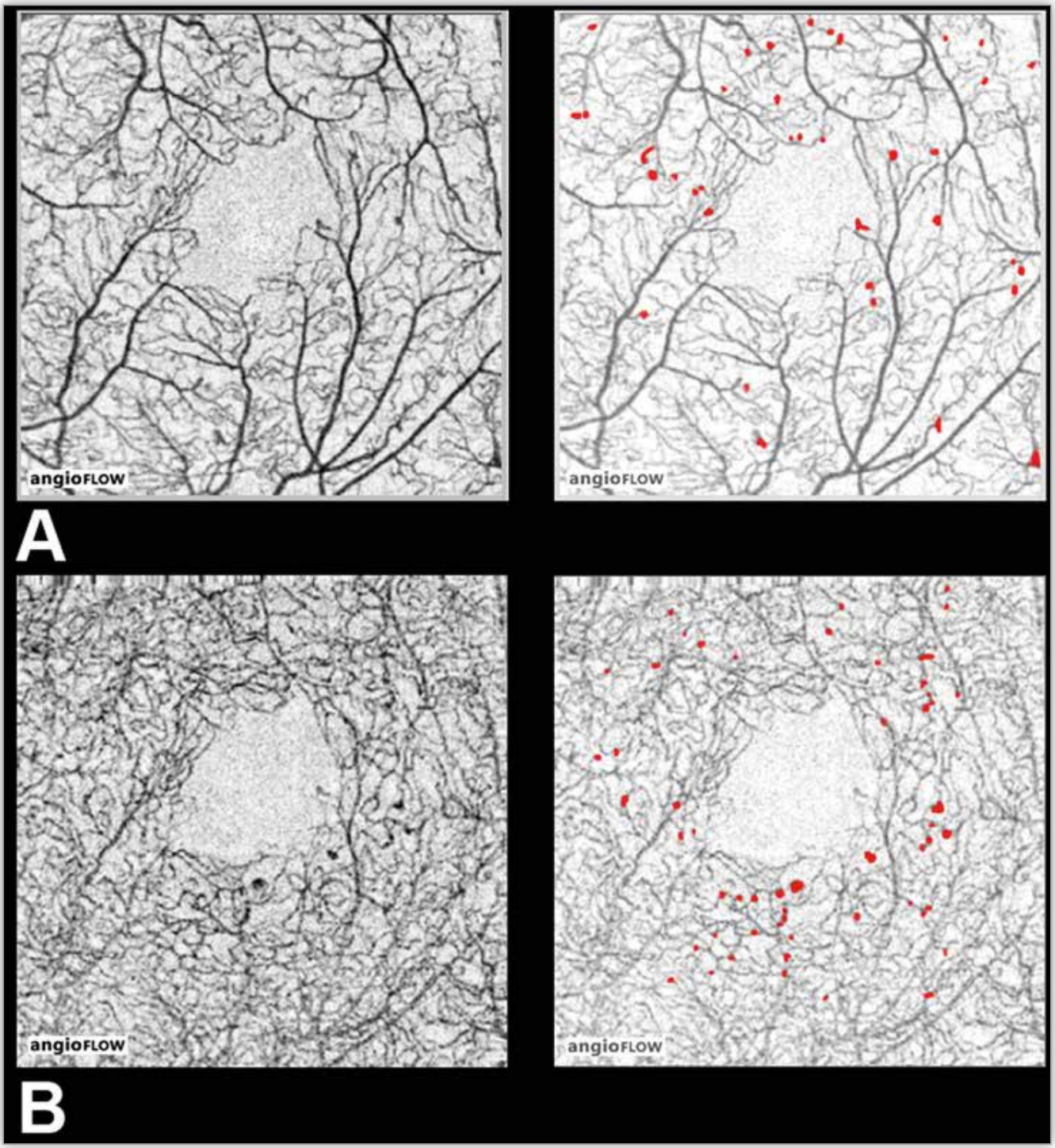

Fig. 2. Two examples of vascular changes visible in angioflow OCT scans.
A decrease in vascular density, enlargement of FAZ area, as well as microaneurysms (marked in red) (A), irregularity of vascular density, enlargement of FAZ area, as well as microaneurysms (marked in red) (B).

Ryc. 2. Dwa przykłady zmian naczyniowych widocznych w trybie „angioflow" OCT.
Widoczne: rozrzedzenie sieci naczyń, poszerzenie strefy FAZ oraz mikrotętniaki (zaznaczone na czerwono) (A), nierównomierna gęstość sieci naczyń, poszerzenie strefy FAZ oraz mikrotętniaki (zaznaczone na czerwono) (B).

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were performed for the significance level $\alpha = .05$ using Microsoft Excel and AddinsoftXLStat 2008 software. A *p* value below .05 was considered statistically significant.

Results

The total superficial retinal capillary network area in the macula was significantly ($p < .0001$) smaller in diabetic patients (22.257 ± 6.316) pixels than in healthy subjects (28.355 ± 3.793 pixels) (Fig. 3).

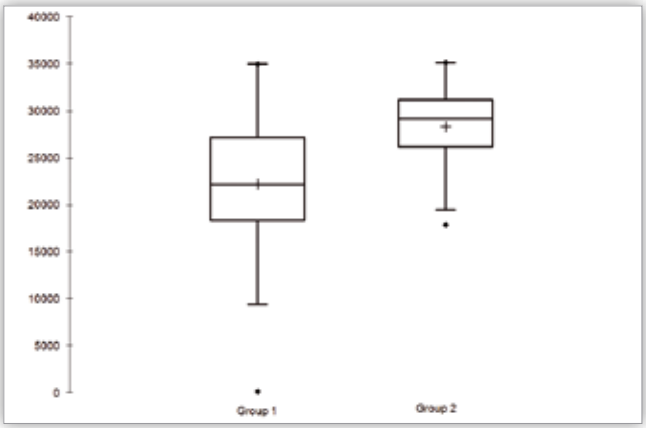

Fig. 3. Retinal superficial capillary network area (pixels).
The total superficial retinal capillary network area in the macula was significantly ($p < .0001$) smaller in diabetic patients (group 1) than in healthy subjects (group 2).

Ryc. 3. Powierzchnia (piksele) powierzchownej sieci naczyń krwionośnych siatkówki.
U chorych na cukrzycę (grupa 1.) całkowita powierzchnia naczyń krwionośnych powierzchownej warstwy naczyń w plamce była istotnie mniejsza niż u osób zdrowych (grupa 2.). Różnica była istotna statystycznie ($p < 0{,}0001$).

The total superficial retinal capillary network length in the macula was significantly ($p < .0001$) smaller in diabetic patients (9.313 ± 2.790 pixels) than in healthy subjects (11.360 ± 1.809 pixels) (Fig. 4).

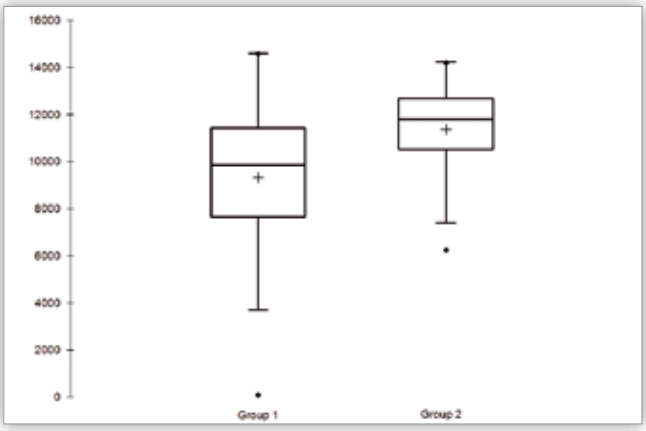

Fig. 4. Retinal superficial capillary network length (pixels).
The total superficial retinal capillary network length in the macula was significantly ($p < .0001$) smaller in diabetic patients (group 1) than in healthy subjects (group 2).

Ryc. 4. Długość (piksele) powierzchownej sieci naczyń krwionośnych siatkówki.
U chorych na cukrzycę (grupa 1.) całkowita długość naczyń krwionośnych powierzchownej warstwy naczyń w plamce była istotnie mniejsza niż u osób zdrowych (grupa 2.). Różnica była istotna statystycznie ($p < 0{,}0001$).

The total deep retinal capillary network area in the macula was significantly ($p < .0001$) smaller in diabetic patients (32.134 ± 8.926 pixels) than in healthy subjects (41.318 ± 5.247 pixels) (Fig. 5).

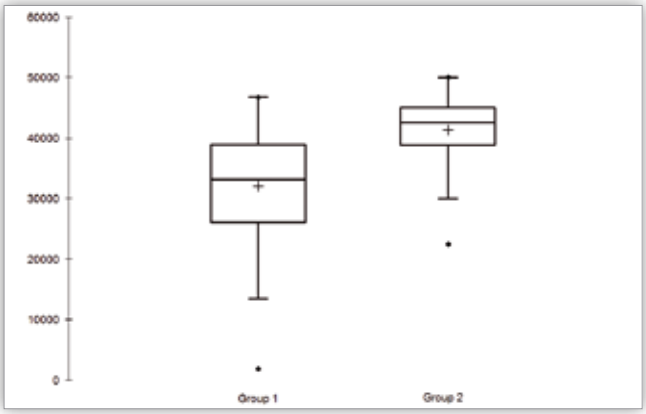

Fig. 5. Retinal deep capillary network area (pixels).
The total deep retinal capillary network area in the macula was significantly ($p < .0001$) smaller in diabetic patients (group 1) than in healthy subjects (group 2).

Ryc. 5. Powierzchnia (piksele) głębokiej sieci naczyń krwionośnych siatkówki.
U chorych na cukrzycę (grupa 1.) całkowita powierzchnia naczyń krwionośnych głębokiej warstwy naczyń w plamce była istotnie mniejsza niż u osób zdrowych (grupa 2.). Różnica była istotna statystycznie ($p < 0{,}0001$).

The total deep retinal capillary network length in the macula was significantly ($p < .0001$) smaller in diabetic patients (14.282 ± 3.416 pixels) than in healthy subjects (16.909 ± 1.619 pixels) (Fig. 6).

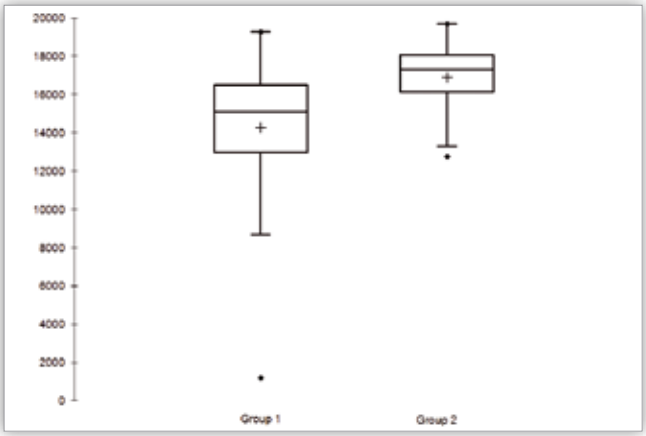

Fig. 6. Retinal deep capillary network length (pixels).
The total deep retinal capillary network length in the macula was significantly ($p < .0001$) smaller in diabetic patients (group 1) than in healthy subjects (group 2).

Ryc. 6. Długość (piksele) głębokiej sieci naczyń krwionośnych siatkówki.
U chorych na cukrzycę (grupa 1.) całkowita długość naczyń krwionośnych głębokiej warstwy naczyń w plamce była istotnie mniejsza niż u osób zdrowych (grupa 2.). Różnica była istotna statystycznie ($p < 0.0001$).

There was no difference ($p > .05$) in the total capillary network area in the outer retina between diabetic (4.211 ± 6.799 pixels) and healthy subjects (2.512 ± 4.529 pixels). There was no difference ($p > .05$) in the total capillary network

length in the outer retina between diabetic patients (3.567 ± 11.950 pixels) and healthy subjects (1.464 ± 2.575 pixels). The total choriocapillaris vascular network area in the macula was significantly ($p < .0001$) smaller in diabetic patients (45.417 ± 7.036 pixels) than in healthy subjects (49.726 ± 4.874 pixels). There was no difference ($p > .05$) in the total vascular network length in the choriocapillaris between diabetic patients (20.551± 2.980 pixels) and healthy subjects (21.105 ± 2.766 pixels).

Table I shows morphological changes in the superficial retinal capillary network. The prevalence of vascular morphological changes in the superficial capillary network was significantly ($p < .0001$) higher in diabetic patients than in healthy subjects, which is a sign of vascular remodeling. Table II shows morphological changes in the deep retinal capillary network. The prevalence of vascular morphological changes in the deep capillary network was significantly ($p < .0001$) higher in diabetic patients than in healthy subjects, which is a sign of vascular remodeling.

Discussion

With time, most diabetic patients will develop some form of microangiopathy, which reflects the altered anatomy, morphology and function of microvascular network. Microangiopathy affects all bodily organs and can be easily visualized in the eye fundus. Diabetic retinopathy is the main cause of blindness in patients with diabetes. Furthermore, it is one of the most frequent causes of vision loss among working-age adults worldwide (5).

Early detection of morphological retinal vascular changes significantly impacts further treatment. Until now, FA has been the gold standard of the retinal vascular imaging (6). OCT-A is a new non-invasive method of analyzing retinal and choroidal circulation. It is based on high-resolution imaging of the blood vessels. The main advantage of this technology is the fact that no dye injection is necessary. Conventional FA can only visualize blood vessels in a nearly transparent, hundred-micrometer thick structure. It provides good images of the superficial retinal capillary network but not of the deep capillary layer. In contrast, OCT-A provides images of both the superficial and deep retinal vascular plexuses which can be evaluated independently (7). The main limitations of OCT-A include small scan size (3 mm x 3 mm or 4.5 mm x 4.5 mm) and the ability to only scan the posterior pole. Also, clear optic media and clear, well-hydrated cornea are the necessary prerequisites of effective OCT-A assessment. Therefore, it may be difficult or impossible to examine patients with corneal opacities and oedema, cataracts, vitreous hemorrhage or hazy vitreous. Scans can be performed with a non-dilated pupil, but mydriasis is very helpful. The same limitations apply to FA.

	Group 1/ Grupa 1.		Group 2/ Group 2.	
Superficial vascular network/ Powierzchowna sieć naczyń krwionośnych siatkówki	**n**	**%**	**n**	**%**
regular/ regularna	**36**	40	**44**	63
irregular/ nieregularna	**54**	60	**26**	37
Density of capillaries/ Gęstość sieci naczyń włosowatych				
dense/ gęsta	**30**	33	**54**	77
medium dense/ średnio gęsta	**44**	49	**16**	23
rare/ przerzedzona	**16**	18	**0**	0
Microaneurysms/ Mikrotętniaki				
no microaneursysms/ brak	**52**	58	**66**	94
single microaneursysms/ pojedyncze	**33**	37	**4**	6
multiple microaneursysms/ liczne	**5**	6	**0**	0
Ischemic areas/ Obszary niedokrwienne				
no ischemic areas/ brak	**65**	72	**70**	100
single ischemic area/ pojedyncze	**18**	20	**0**	0
multiple Ischemic areas/ liczne	**7**	8	**0**	0
IRMA				
no IRMAs/ brak	**8**	9	**70**	100
single IRMA/ pojedyncze	**51**	57	**0**	0
multiple IRMAs/ liczne	**31**	34	**0**	0

Different morphological changes in the superficial capillary network were significantly ($p < .0001$) more prevalent in diabetic patients (group 1) than in healthy subjects (group 2). / Różne zmiany morfologiczne w obrębie powierzchownej sieci naczyń krwionośnych siatkówki występowały istotnie ($p < 0{,}0001$) częściej w grupie pacjentów z cukrzycą (grupa 1) niż u zdrowych ochotników (grupa 2).
IRMA – intraretinal microvascular abnormalities/ śródsiatkówkowe nieprawidłowości drobnonaczyniowe.

Tab. I. Morphological changes in the blood vessels of the superficial retinal vascular network in both groups.
Tab. I. Zmiany morfologiczne w powierzchownej sieci naczyń krwionośnych siatkówki u badanych z obu grup.

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	Group 1/ Grupa 1.		Group 2/ Grupa 2.	
Deep vascular network/ Głęboka sieć naczyń krwionośnych	**n**	**%**	**n**	**%**
regular/ regularna	**42**	47	**41**	59
irregular/ nieregularna	**48**	53	**29**	41
Density of capillaries/ Gęstość sieci naczyń włosowatych				
dense/ gęsta	**35**	39	**41**	49
medium dense/ średnio gęsta	**26**	29	**27**	39
rare/ przerzedzona	**29**	32	**2**	3
Microaneurysms/ Mikrotętniaki				
no microaneursysms/ brak	**42**	47	**66**	94
single microaneursysms/ pojedyncze	**34**	38	**4**	6
multiple microaneursysms/ liczne	**14**	16	**0**	0
Ischemic areas/ Obszary niedokrwienne				
no ischemic areas/ brak	**52**	58	**70**	100
single ischemic area/ pojedyncze	**27**	30	**0**	0
multiple ischemic areas/ liczne	**11**	12	**0**	0
IRMA				
No IRMAs/ brak	**8**	9	**70**	100
single IRMA/ pojedyncze	**58**	64	**0**	0
multiple IRMAs/ liczne	**24**	27	**0**	0

Different morphological changes in the deep capillary network were significantly ($p < .0001$) more prevalent in diabetic patients (group 1) than in healthy subjects (group 2). / Różne zmiany morfologiczne w obrębie głębokiej sieci naczyń krwionośnych siatkówki występowały istotnie ($p < 0{,}0001$) częściej w grupie pacjentów z cukrzycą (grupa 1) niż u zdrowych ochotników (grupa 2).
IRMA – intraretinal microvascular abnormalities/ śródsiatkówkowe nieprawidłowości drobnonaczyniowe.

Tab. II. Morphological changes in the blood vessels of the deep retinal vascular network in both groups.
Tab. II. Zmiany morfologiczne w głębokiej sieci naczyń krwionośnych siatkówki u badanych z obu grup.

OCT-A is a useful examination in other diseases, such as retinal neovascularization (8), retinal venous occlusions (7), senile and juvenile macular degenerations (9) or glaucoma (10). The condition of the retinal and choroidal vascular network provides indirect information about the general state of blood vessels in the entire body. Thus, OCT-A may be a valuable diagnostic method in many systemic disorders, such as atherosclerosis, hypertension, metabolic syndrome, stroke and other cerebrovascular diseases like myocardial infarction, peripheral arterial disease, renal dysfunction or vascular malformations (11).

Recently, OCT-A has been evaluated by many authors also in patients with diabetic retinopathy (2–4). In this study, however, we tried to measure and analyze parameters such as vascular network length and area which have never been evaluated by any author. These parameters can be easily derived from the OCT examination by means of image processing. In our opinion, these parameters may play a valuable role in interpreting OCT-A findings. Vascular network length and area as well as morphological changes are results of capillary remodeling which occurs in diabetic patients. The advantage of using these parameters over the subjective grading of the vascular changes (which is currently done) is their being measurable (and thus objective), which enables a more precise comparative analysis.

In this study, we found that the total capillary network area and length, both in superficial and deep vascular plexus of the macula, was significantly smaller in diabetic patients than in healthy subjects. Furthermore, patients with diabetes often present with morphological anomalies of the superficial and deep retinal vessels. They also have a smaller area of vascular network in the choriocapillaris, as compared to healthy subjects. Our results are consistent with those presented to date by other authors.

Interestingly, we found that outer retinal capillary network area and length were detectable, but similar in both groups. Although black pixels were visible in outer retinal scans, it should be emphasized that their pattern did not correspond to a pattern of vessels bur resembled randomly scattered points. As normal outer retina is avascular, the calculated black pixels visible in these scans most probably resulted from noise generated by the device, or not entirely precise echo of vascular network of the choriocapillaris. This is additionally supported by the fact that the number of black pixels visible in outer retinal scans is only a small fraction of black pixels corresponding to blood vessels in retinal superficial and retinal deep capillary network areas.

Couturier et al. (3) found that diabetes-related anomalies were detectable in both superficial and deep capillary plexus

and that OCT-A is superior to FA in assessing capillary nonperfusion areas. De Carlo et al. (12) have pointed out that OCT-A may reveal foveal microvascular changes even in diabetic patients with no clinical manifestation of diabetes. Takase et al. (13) found that morphological anomalies in the macula are present in diabetic eyes prior to DR becoming manifest and detectable. We agree with their findings by showing that the total vascular length and area are smaller in diabetic patients than in healthy subjects.

In their study in a small group of 12 patients, Hwang et al. (14) found that participants with DR had reduced parafoveal and perifoveal vessel density and a greater total avascular area and foveal avascular zone area as compared to healthy controls. Agemy et al. (15) found that capillary perfusion density values were significantly lower in nearly all layers of diabetic patients, when compared with controls. Trend analysis showed a significant decrease in capillary perfusion density values with the progression of DR. The authors concluded that quantitative retinal vascular perfusion density mapping may offer an objective method for monitoring disease progression in DR.

Conclusions

OCT-A is a useful tool which easily reveals the presence of microvascular changes in diabetic patients. Total retinal capillary network area and retinal capillary network length can be utilized to numerically describe the severity of vascular abnormalities and they are found to be significantly smaller in diabetic patients both in the superficial and deep retinal layers. Similarly, choriocapillaris vascular network area, but not length, is significantly smaller in diabetic patients, in comparison with healthy subjects. Morphological vascular changes, such as decreased vascular density, regularity of capillary network, m croaneurysms, ischemic areas, IRMA, neovascularizations and remodeling of retinal capillaries, are more commonly detected on the angio-OCT scans of diabetic eyes, both in the superficial and in the deep retinal plexus, than in non-diabetic, healthy eyes of controls. OCT-A can be used for non-invasive evaluation of retinal vessels as it helps detect vascular changes typical of DR.

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Reprint requests to (Adres do korespondencji):
Maria Jędrzejak, MD
Department of Ophthalmology, Medical University of Lódź
Barlicki University Hospital No.1
Kopcińskiego 22, 90-153 Lodz, Poland
e-mail: wagrowska.marysia@gmail.com

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